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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,428	07/16/2003	Dieter Heindl	21329-US	8931

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,428	HEINDL ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *18-23,32,34,35 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-23,32,34,38 and 39* is/are rejected.

7)☒ Claim(s) *35 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE filed on November 14, 2005 and the amendment filed on September 30, 2005 have been entered. The claims pending in this application are claims 18-23, 32, 34, 35, and 37-39. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on September 30, 2005.

Claim Objections

2. Claim 35 objected to because of the following informality: "a 3 oligonucleotides" should be "3 oligonucleotides".

3. Claim 39 objected to because of the following informality: there should be a coma between "a nucleic acid amplification primer" and "a template dependent nucleic acid polymerase" in lines 3 and 4 the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

Regarding claim 22, since Nazarenko *et al.*, teach a upstream hairpin primer comprising a fluorescent dye FAM and a quencher (ie., DABCYL) (see column 38 and Figures 24A to G) and a reverse primer labeled with a fluorescent dye rhodamine (see column 35, lines 29-37 and Figure 13A), it is known that FAM is a suitable donor for rhodamine (see column 18) and claims 18 and 22 do not require that a first single stranded oligonucleotide is a complete single stranded oligonucleotide, Nazarenko *et al.*, disclose that first oligonucleotide (ie., the partial single stranded upstream hairpin primer) carrying a FRET donor entity (ie., FAM) and at least one second entity (ie., the quencher), said second entity being a compound (ie., DABCYL) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and a second oligonucleotide (ie., the reverse primer) carrying a FRET acceptor entity (ie., rhodamine) but not carrying a FRET donor entity as recited in claim 18. Since claim 22 is a composition comprising a nucleic acid sample (ie., a template used for PCR PSA cDNA) and the first and second oligonucleotides (ie., the upstream hairpin primer and the reverse primer) according to claim 18, Nazarenko *et al.*, disclose claim 22.

Therefore, Nazarenko *et al.*, teach all limitations recited in claim 22.

Response to Arguments

In page 6, third paragraph bridging to page 7, second paragraph of applicant's remarks, applicant argues "[T]he present claims, as amended, are directed to a kit comprising a plurality of oligonucleotides of specified structure. Nazarenko et al. does not describe a kit or composition or even experiment that was carried out in which the hairpin primer and the reverse primer referred to in the office action were used together. The hairpin primer described in column 38 was used with a standard (not labeled) reverse primer (SEQ ID NO:12), not a primer comprising rhodamine. See, e.g., Nazarenko *et al.,* column 38, lines 15-17. Thus, at most, Nazarenko *et al.* describes use of the hairpin primer labeled with a dye and a quencher but without further labeling of the reverse primer. The experiment described in column 35 of Nazarenko et al. does indeed involve a primer comprising rhodamine, but does not involve the hairpin primer. Instead, column 35 describes an experiment to determine if labeling of a reverse primer blocks incorporation of dNTP".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because the claims do not require that all probes recited in claims 18 and 23 or claim 20 must be used together.

6. Claims 22 and 38 is rejected under 35 U.S.C. 102(e) as being anticipated by Frutos *et al.,* (US Patent No. 6,579,680 B2, priority date: February 28, 2000).

Regarding claim 22, since Frutos *et al.,* teach that a single stranded SEQ ID NO: 4 comprising a quencher and 5-nitroindole and a single stranded SEQ ID No: 3 comprising a fluorescent dye cy3 (see column 7) and a quencher can be a fluorescent dye such as ROX (see

column 5, lines 40-64 and column 10, lines 23-50), and ROX can work as a fluorescent donor for a non-fluorescent quencher while cy3 can work as an acceptor of another fluorescent donor such as Green fluorescent protein (GFP), Frutos *et al.,* disclose that first oligonucleotide (ie., the oligonucleotide comprising ROX and 5-nitroindole) carrying a FRET donor entity (ie., ROX) and at least one second entity (ie., the nitroindole moiety), said second entity being a compound (ie., nitroindole moiety) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., ROX) and a second oligonucleotide (ie., the oligonucleotide labeled a fluorescent dye cy3) carrying a FRET acceptor entity (ie., cy3) but not carrying a FRET donor entity as recited in claim 18. Since Frutos *et al.,* also teach a complementary unlabeled sequence (see column 7) and claim 22 is a composition comprising a nucleic acid sample (ie., the complementary unlabeled sequence) and the first and second oligonucleotides (ie., the oligonucleotide comprising ROX and 5-nitroindole and the oligonucleotide labeled a fluorescent dye cy3) according to claim 18, Frutos *et al.,* disclose claim 22.

Regarding claim 38, since Frutos *et al.,* teach that a single stranded SEQ ID NO: 4 comprising a quencher and 5-nitroindole and a single stranded SEQ ID No: 3 comprising a fluorescent dye cy3 (see column 7) and a quencher can be a fluorescent dye such as ROX (see column 5, lines 40-64 and column 10, lines 23-50), and ROX can work as a fluorescent donor for a non-fluorescent quencher while cy3 can work as an acceptor of another fluorescent donor such as Green fluorescent protein (GFP), Frutos *et al.,* disclose first oligonucleotide (ie., the oligonucleotide comprising ROX and 5-nitroindole) carrying a FRET donor entity (ie., ROX) and a nitroindole moiety capable of quenching fluorescence emission of said FRET donor entity (ie., ROX) and a second oligonucleotide (ie., the oligonucleotide labeled a fluorescent dye cy3)

carrying a FRET acceptor entity (ie., cy3) as recited in claim 32. Since Frutos *et al.,* also teach a complementary unlabeled sequence (see column 7) and claim 38 is a composition comprising a nucleic acid sample (ie., the complementary unlabeled sequence) and a pair of hybridization probes (ie., the oligonucleotide comprising ROX and 5-nitroindole and the oligonucleotide labeled a fluorescent dye cy3) according to claim 32, Frutos *et al.,* disclose claim 38.

Therefore, Frutos *et al.,* teach all limitations recited in claims 22 and 38.

Response to Arguments

In page 7, third to sixth second paragraphs of applicant's remarks, applicant argues that the amendments have overcome the rejection.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Frutos *et al.,* teach claims 22 and 38 (see above rejection).

7. Claims 22 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Frutos *et al.,* (Journal of American Chemical Society, 124, 2396-2397, March 2002).

Regarding claim 22, since Frutos *et al.,* teach that a single stranded probe Y comprising a ROX and 5-nitroindole and a single stranded probe X comprising a fluorescent dye cy3 (see page 2396, left column and Scheme 1) and ROX can work as a fluorescent donor for a non-fluorescent quencher while cy3 can work as an acceptor of another fluorescent donor such as Green fluorescent protein (GFP), Frutos *et al.,* disclose that first oligonucleotide (ie., probe Y comprising ROX and 5-nitroindole) carrying a FRET donor entity (ie., ROX) and at least one second entity (ie., the nitroindole moiety), said second entity being a compound (ie., nitroindole moiety) which is capable of quenching fluorescence emission of said donor fluorescent entity

(ie., ROX) and a second oligonucleotide (ie., probe X labeled a fluorescent dye cy3) carrying a FRET acceptor entity (ie., cy3) but not carrying a FRET donor entity as recited in claim 18. Since Frutos *et al.,* also teach a complementary unlabeled sequence (see Figure 1) and claim 22 is a composition comprising a nucleic acid sample (ie., the complementary unlabeled sequence) and the first and second oligonucleotides (ie., probe Y comprising ROX and 5-nitroindole and probe X labeled a fluorescent dye cy3) according to claim 18, Frutos *et al.,* disclose claim 22.

Regarding claim 38, since Frutos *et al.,* teach that a single stranded probe Y comprising a ROX and 5-nitroindole and a single stranded probe X comprising a fluorescent dye cy3 (see page 2396, left column and Scheme 1) and ROX can work as a fluorescent donor for a non-fluorescent quencher while cy3 can work as an acceptor of another fluorescent donor such as Green fluorescent protein (GFP), Frutos *et al.,* disclose first oligonucleotide (ie., probe Y comprising ROX and 5-nitroindole) carrying a FRET donor entity (ie., ROX) and a nitroindole moiety capable of quenching fluorescence emission of said FRET donor entity (ie., ROX) and a second oligonucleotide (ie., probe X labeled a fluorescent dye cy3) carrying a FRET acceptor entity (ie., cy3) as recited in claim 32. Since Frutos *et al.,* also teach a complementary unlabeled sequence (see Figure 1) and claim 38 is a composition comprising a nucleic acid sample (ie., the complementary unlabeled sequence) and a pair of hybridization probes (ie., probe Y comprising ROX and 5-nitroindole and probe X labeled a fluorescent dye cy3) according to claim 32, Frutos *et al.,* disclose claim 38.

Therefore, Frutos *et al.,* teach all limitations recited in claims 22 and 38.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 18-21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko *et al.,* as applied to claim 22 above, and further in view of Stratagene catalog (page 39, 1988).

The teachings of Nazarenko *et al.,* have been summarized previously, *supra.*

Regarding claim 18, as shown the rejection under 35 U.S.C 102 (b), Nazarenko *et al.,* teach a first single stranded oligonucleotide and a second single stranded oligonucleotide recited in claim 18.

Regarding claim 20, since Nazarenko *et al.,* teach a upstream hairpin primer comprising a fluorescent dye FAM and a quencher (ie., DABCYL), a downstream primer (see column 38 and Figures 2, 3, 24A to G) and a reverse primer labeled with a fluorescent dye rhodamine (see

column 35, lines 29-37 and Figure 13A), and it is known that FAM is a suitable donor for rhodamine (see column 18) and claim 20 does not require that the third oligonucleotide of claim 20 must be different from the second oligonucleotide of claim 18, Nazarenko *et al.*, disclose a first oligonucleotide and a second oligonucleotide (ie., the partial single stranded upstream hairpin primer and downstream primer) capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide (ie., the upstream hairpin primer) and a third oligonucleotide (ie., the reverse primer) are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity (ie., FAM) and a FRET acceptor entity (ie., rhodamine) wherein the oligonucleotide (ie., the upstream hairpin primer) carrying the FRET donor entity (ie., FAM) further carries at least one second entity (ie., the quencher), said second entity being a compound (ie., DABCYL) which is capable of quenching fluorescence emission of said donor fluorescent entity (ie., FAM) and wherein the oligonucleotide (ie., the reverse primer) carrying the FRET acceptor entity (ie., rhodamine) does not carry a FRET donor entity as recited in claim 20.

Regarding claims 19 and 21, since Nazarenko *et al.*, teach that FAM connects DABCYL by A-hydrogen bond-T (see Figures 24A to G), Nazarenko *et al.*, disclose that the FRET donor entity (ie., FAM) and the second entity (ie., DABCYL) are carried on adjacent nucleotides of the first oligonucleotide (ie., the upstream hairpin primer) as recited in claims 19 and 21.

Regarding claim 23, since a pair of hybridization probes recited in claim 23 is identical to a first single stranded oligonucleotide and a second single stranded oligonucleotide recited in claim 18, Nazarenko *et al.*, teach a pair of hybridization probes recited in claim 23. Since Nazarenko *et al.*, also teach a kit comprising a hairpin primer, a DNA polymerase and a buffer

for PCR reaction (see columns 32 and 33), Nazarenko *et al.,* disclose at least one other component (ie., the DNA polymerase) as recited in claim 23.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probes of claims 18 and 23 or 3 oligonucleotides of claim 20 and at least one other component such as a template dependent nucleic acid polymerase (ie., the DNA polymerase) taught by Nazarenko *et al.,* into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "[E]ach kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

Response to Arguments

In page 7, last paragraph bridging to page 8, second paragraphs of applicant's remarks, applicant argues that "[N]azarenko et al. does not in fact teach or suggest all of the components of the kit recited in claim 23. The Stratagene catalog does not address these omissions. Therefore, the cited references, separately or in combination, do not teach or suggest all of the elements of the claims".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Nazarenko *et al.,* do teach all of the components recited in claim 23 (see above rejection). Furthermore, applicant does not indicate which component recited in claim 23 is not taught by Nazarenko *et al.*.

10. Claims 18, 19, 32, 34, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frutos *et al.,* (2000) as applied to claims 22 and 38 above, and further in view of Stratagene catalog (page 39, 1988).

The teachings of Frutos *et al.,* have been summarized previously, *supra.*

Regarding claims 18 and 32, as shown the rejection under 35 U.S.C 102 (e), Frutos *et al.,* teach a first single stranded oligonucleotide and a second single stranded oligonucleotide recited in claims 18 and 32.

Regarding claims 19 and 34, since Frutos *et al.,* teach that ROX is located on 3' end of SEQ ID NO: 4 and 5-nitroindole is located on middle portion of SEQ ID NO: 4 (see column 5, lines 40-64 and column 7), Frutos *et al.,* disclose that the FRET donor entity (ie., ROX) and the second entity (ie., 5-nitroindole moiety) are carried on adjacent nucleotides of the first oligonucleotide (ie., SEQ ID No: 4) as recited in claims 19 and 34.

Regarding claim 39, since a pair of hybridization probes recited in claim 39 is identical to a first single stranded oligonucleotide and a second single stranded oligonucleotide recited in claim 32, Frutos *et al.,* teach a pair of hybridization probes recited in claim 39. Since Nazarenko *et al.,* also teach a kit comprising an array with oligonucleotides immobilized thereon (see column 9, lines 41-55) wherein at least one of these oligonucleotides has an ability to serve as a primer, Frutos *et al.,* disclose at least one other component (ie., a nucleic acid amplification primer) as recited in claim 39.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probes of claims 18 and 32 and at least one

other component (ie., a nucleic acid amplification primer) taught by Frutos *et al.,* into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "[E]ach kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. 2) The other service provided in a kit is quality control" (page 39, column 1).

Conclusion

11. Claims 35 and 37 appear to be allowable if applicant can overcome above objection on claim 35 because the prior art in the record does not teach or suggest a kit comprising 3 oligonucleotides comprising a first oligonucleotide and a second oligonucleotide capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction, further characterized in that said first oligonucleotide and a third oligonucleotide are each labeled with one corresponding member of a FRET pair consisting of a FRET donor entity and a FRET acceptor entity, wherein the oligonucleotide carrying the FRET donor entity further carries a nitroindole moiety capable of quenching fluorescence of said FRET donor entity. The patent from Frutos *et al.,* cannot used as a prior art to reject claim 35 since Frutos *et al.,* do not teach a first oligonucleotide and a second oligonucleotide capable of acting as a pair of amplification primers for a template dependent nucleic acid amplification reaction.

12. No claim is allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30

(November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Frank Lu
Primary Examiner
January 31, 2006